# AOARD REPORT

Basic Research Efforts in Japan
- Science and Technology Agency's Exploratory Research for Advanced Technology (ERATO) program



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AOARD

The Research Development Corporation of Japan (JRDC), founded in 1991 as one of the statutory corporations of the Science and Technology Agency (STA), is mandated to serve for STA as an organizer of national R&D projects. JRDC is responsible of identifying new R&D topics, setting up the actual cross-links for coordinating Japanese government, academia and industry interfaces, and managing the actual day-to-day operation of national R&D projects. JRDC's responsibility includes basic research, technology transfer, and inter agency/service research activity. Specifically, in the basic research arena, JRDC is in charge of the basic research program called the Exploratory Research for Advanced Technology (ERATO) program, which started in 1981 for the purpose of enhancing basic research activity in Japan. In 1989 and 1991, the JRDC created two more programs, respectively, called the International Joint Research Program and Precursory Research for Embryonic Science and Technology due to the widely acknowledged success of the ERATO program. With four new projects selected this year and three projects coming to an end, currently there are a total of 23 on-going ERATO projects. Names of newly selected ERATO projects include "Particle Physics" headed by Professor K. Takayanagi of Tokyo Institute of Technology, "Active Glass" headed by Professor K. Hirao of Kyoto University, "Behavior Genes" headed by Dr. D. Yamamoto of Mitsubishi Chemical, and "Biotimer" headed by Professor Y. Takai of Osaka University. This report provides readers with some basic insights to 23 of the on-going ERATO projects, being handled by JRDC to explore basic research in Japan.

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## I. Introduction

In Japan, as one of the industrial nations of the world, the synergistic advancement of science and technology is an important issue concerning future well being of maintaining a strong economic basis in the world market today. It is important for Japanese to maintain technical edge and economic influence over the rest of the world by cultivating new scientific areas and taking up a leadership role of the scientific community in the world. It is exactly for that reason all the Japanese government, academia, and industrial sectors are working together to advance the understanding of scientific knowledge.

The Science and Technology Agency (STA), which reports to the Prime Minister's office, is responsible for handling all the national research and development (R&D) projects in Japan. Projects are set up based on fulfilling national goals requirements and making research in new technical areas such as advanced materials, energy, space, and maritime as well as many other fields of basic sciences. STA has a task of coordinating Japanese science and technology activities by dealing directly with Japanese industry and academia in order to set up national R&D projects. STA is also chartered to handle and coordinate all the federally sponsored international science and technology programs.

The Research Development Corporation of Japan (JRDC), founded in 1991 as one of the statutory corporations of STA, is mandated to serve for STA as an organizer of national R&D projects. JRDC is responsible for identifying new R&D topics, setting up the actual cross-links for coordinating Japanese government, academia and industry interfaces, and managing the actual day-to-day operation of national R&D projects. JRDC's responsibility includes basic research, technology transfer, and inter agency/service research activity. Specifically, in the basic research arena, JRDC is in charge of the basic research program called the Exploratory Research for Advanced Technology (ERATO) program, which started in 1981 for the purpose of enhancing basic research activity in Japan. In 1989 and 1991, the JRDC created two more programs, respectively, called the International Joint Research Program (IJRP) and Precursory Research for Embryonic Science and Technology (PRESTO) due to the widely acknowledged success of the ERATO program. IJRP was established with the intention of promoting international basic research collaboration between Japanese and non-Japanese research institutes within framework of any basic research activities. On the other hand, PRESTO was established specifically in support of promising young Japanese researchers for a period of three years in the area of embryonic research. To accomplish national research goals, STA has provided JRDC with a total operating budget of around 21.6 billion yen (approximately $216 million based on the current conversion rate of 100 yen to a dollar) in Fiscal Year 94.

## II. Exploratory Research for Advanced Technology (ERATO)

For the purpose of fostering advanced technologies and stimulating future interdisciplinary scientific activities in Japan, JRDC initiated an innovative research program called the ERATO program. Normally, research topics considered by the ERATO program cover broad biological and physical science fields. The ERATO program provides Japanese researchers to explore new ideas and concepts by setting up federally-funded basic research projects without having to consider commercial applications of its research by-products as the case for many of the Ministry of International Trade and Industry (MITI) sponsored projects. The intent of ERATO projects is to investigate new and unexplored research areas of science and technology and set up a strong

foundation for the future of basic research activity in Japan.

One of the important tasks performed by JRDC for the ERATO program is the selection of research topics and project leaders. Specifically, research topics and project leaders are selected by the Research and Development Council (RDC), which is the functioning body of JRDC. The RDC members are made up of scientists and professionals representing mostly academic and industrial sectors. The Council selects project leaders based on reputation of scientists who made exceptional scientific contributions in its selected topical fields and have talents in guiding and stimulating young researchers. The thrust of each project comes from the vision of the project leader. The project leaders must have deep insight to the selected topic and has the overall responsibility of executing and managing the project. The project leaders are charged with the sole responsibility of recruiting, selecting, and directing the project team members. Usually, each project team is made up of approximately 25 persons, consisting of 15 to 20 scientists in three technical groups and the remainder for supporting staffs. With the help of JRDC, the project leaders seek for academic and industrial participants. In an effort to tap creative minds of young scientists, the project leaders select a heterogeneous mixture of young PhDs researchers who are in early thirties and have some or no professional experience in individual sectors. Reflecting the past 800 young PhD researchers who have participated in ERATO, 350 came with some industrial experience and 450 with no experience. To reflect the international participation, twenty percent of the total researchers came from abroad. In general, ERATO projects are stimulating creative minds of young PhD scientists and serving as the fertile ground for training the future professional leaders in Japan.

Currently, as of 1994, twenty-three ERATO projects are in progress at various stages of the five year project as shown in Table 1 (i.e., three projects selected for 1989-1994, and four projects selected every year between 1990 and 1994). Names of four project selected for this year included "Particle Physics" headed by Professor K. Takayanagi of Tokyo Institute of Technology, "Active Glass" headed by Professor K. Hirao of Kyoto University, "Behavior Genes" headed by Dr. D. Yamamoto of Mitsubishi Chemical, and "Biotimer" headed by Professor Y. Takai of Osaka University. Total funding levels of these projects normally range from 1.5 to 2.0 billion yen (US$15 - 20 million) for a period of five years. Thus far, eighteen projects have been completed since the ERATO program started in 1981 as shown in Table 2. All the ERATO project team members are employed directly by JRDC on annual basis with the contract renewed every year for duration of the project. Topics considered for ERATO research projects are publicly announced in the early summer of each year along with employment information for young PhD scientists and engineers to participate in projects. Open symposia are held in the fall of each year to inform the public for the selection of new ERATO projects and make brief presentations of the projects. The open symposia are also used to present the status of on-going ERATO projects.

In order to maintain flexibility, JRDC has no research facilities of its own. Hence, it is customary for projects to be operated out of some laboratory space which is provided free of charge by academic and industrial institutions. Consequently, it is possible that the project can be operated out of several scattered locations. However, it normally happens that the laboratory space, where the selected project leader has been working on the past, turns out to be the main research facility of the project. To assure proper communications, JRDC headquarters, project managing offices, and research facilities are linked by a communications network.

The results of projects are the common property of JRDC and members of the project team. Patents rights are shared equally by both JRDC (50%) and project members (50%). Any portion of the patent right, which belongs to members, can be transferred to their home institutions

upon completion of the project. Research data are kept in official JRDC laboratory notebooks for any future use and references.

## III. International Joint Research Program (IJRP) and Precursory Research for Embryonic Science and Technology (PRESTO)

The success of the ERATO program has led to the launching of two new programs called the International Joint Research Program (IJRP) in 1989 and Precursory Research for Embryonic Science and Technology (PRESTO) in 1991. PRESTO provides financial supports for a period of five years to individual young researchers who want to carry out embryonic research. Eight new PRESTO projects have been added each year. IJRP is an international version of the ERATO program, supporting five year co-sponsored joint research projects on a 50-50 cooperative basis with Japanese and overseas public organizations. Currently, five IJRP projects are in place participated by four foreign universities and research institutes (UK, USA., Sweden, and France).

## IV. Description of Active ERATO Projects

Described below are twenty-three of the on-going ERATO projects in reverse chronological order as appeared in ERATO brochure.

### 1) Takayanagi Particle Surface (1994-1999)

*Background*

When a crystal is cleaved, many bonds are broken at the surface, and electrons are forced to have a different bonding nature from inside of the crystal. Then, the surface of the crystal will reconstruct itself to a new atomic arrangement and electron energy states which are quite different from that of the bulk crystal underneath.

Now imagine a small particle of nanometer scale, containing hundreds, or several thousands of atoms. At this size the surface dominates. Thus, nanometer scale particles may have different properties from any bulk crystals because of their surface layer. In a particle of a thousand atoms, about 50 percent of the atoms are on the surface layer, indeed.

By taking the view that the surface atoms are identical to that of the underlying bulk atoms, researches until now has achieved several important results. For example, magic number found for tiny clusters is a concept that the metal cluster has a closed shell structure of electron orbitals like those in an atomic nucleus. In recent years, quantum effects specific for electron waves confined in a narrow space, mesoscopic phenomena, attract much interests.

The science of particles has reached a stage in which it is appropriate to distinguish between surface atoms and bulk atoms, and utilize their surface properties. When surface structure of mesoscopic particles differs from their insides, they composed with a core particle and surface layer can be viewed as a nanocapsule, indeed. And the surface layer behaves as a new material surface.

*Research Strategy*

Takayanagi Particle Surface project focuses on the surface of well-defined particles containing hundreds to several thousands of atoms, and research their atomic structures and mesoscopic properties in relationship to their nanoscale sizes.

Takayanagi Particle Surface project is divided into three groups: 1) Basic Structure Group, 2) Quantum Property Group, and 3) Design and Synthesis Group.

The first group studies the rules that govern surface structures, their atomic makeup and

(mesoscopic) potentials. The group uses real-time high-resolution electron microscopy for structure studies. Scanning probe and holograph microscopy will be used for study of electron states to uncover how the reconstructed surface layer generates the electron states in it.

The second group tries to find specific quantum properties such as light emission associated with the surface. The research chiefly uses computer calculations on surface structure and electron states for some representative systems, e.g., semiconductor particles. This research also tries spectroscopic measurements on single or small number of well-defined particles supported on a substrate.

The third group directs itself at the design and synthesis of well-defined mesoscopic particles using cluster beams and other methods. Synthesis of capsule structures will be aimed to find new mesoscopic properties. Research will experiment with particles which can exist outside of vacuum in more practical media.

**2) Hirao Active Glass (1994-1999)**

*Background*

The Hirao Active Glass project will take a view that understanding of the effects of electric fields and other external fields such as magnetic fields on glass is a key to making optical computing elements. The project will examine various types of glass under applied fields to understand basic physical principles behind optical computing.

The recent work shows that the glass center of symmetry can be broken to achieve new active roles. If high voltage is applied across a glass plate at high temperature and the glass is cooled, the resulting glass has the property of converting infrared laser to visible, blue, green and yellow light. This is an active function. The glass somehow combines the energy of two light photons into one photon.

Another work reported that photochemical hole burning materials can be made into glass and exhibit stable properties at room temperature. In photochemical hole burning, narrow bands of color are selectively burned out of reflective coatings. The storage capacity of the coating is multiplied by the number of colors that can be selectively removed and detected. The number is estimated to be around one hundred. It might be possible to multiply this storage capacity by another hundredfold by applying the electric voltage.

The physical mechanism is not known for explaining the effect of applied electric field to glass. Evidently, the electric field induces changes in electronic structure which then produces the active effects.

*Research Strategy*

The project is organized into three groups: 1) Functional Development Group, 2) Structure Formation Group, and 3) Functional Design Group.

A thrust of the first group is to understand basic electronic structures induced by applying external fields. The second group focuses in learning the process of coming up with desired electronics structures by applying external electric and magnetic fields, as well as pulsed laser, ultrasound, and electron beams. The third group works in computer simulations of new glass structures in order to understand basic physics and functions of practical design tools needed to come up with optical computing materials.

## 3) Yamamoto Behavior Genes (1994-1999)

### *Background*

Darwin, in his theory of evolution, postulated that there are two fundamental drives of evolution. The first is survival. The second is the selection of male mates by females. Evolution has produced elaborate anatomical features and behavior that can only be related to making males attractive to females. An example of such an anatomical feature is the plumage of the peacock which has no function in survival and exists only for attracting females. An example of such a behavior is the lek system in certain insects, birds and mammals. In this mating system, males form territories are called leks. The females move from lek to tek until they select a mate. A lek contains no food or anything else useful for the female's survival, only a male. This behavior exists only for the purpose of mate selection.

Since mating behavior is so closely tied to evolution, a similar set of genes should be found in the rest of animals. The Yamamoto Behavior Genes project has chosen mating behavior as a good starting point for researching the molecular genetics of behavior.

### *Research Strategy*

The project will concentrate on the fruit fly Drosophila melanogaster, the animal most useful in genetic studies. A few mating behavior mutants of Drosophila are already known. In the spinster mutation, females very strongly reject courting males. The satori mutation produces homosexual males. The croaker males produce aberrant courtship songs. These mutants are the starting point of the Yamamoto Behavior Genes project's search for the genetics of behavior.

An early goal of the project will be to increase the number of known behavioral mutants in Drosophila. Researchers will also seek secondary mutations in which the original mutation is suppressed or enhanced. These mutations will be used to make a map of behavior genes on the genome, then for cloning the relevant cDNAs. From the clones the project will learn about the proteins which are coded by behavior genes.

In a second area of research, the project will study the anatomy of behavior gene expression. Researchers will use genetic mosaics to identify the critical cells in which the gene products play crucial roles in controlling mating behavior. For example, the gene related to the satori mutation is selectively expressed in a subset of cells in the brain. By replacing wild type cells with mutant counterparts and examining the individual mosaics for their mating behavior, it will be possible to specify single cells that determine the sexual orientation of the fly. Researchers will also study the biochemical basis for the gene's action in these cells.

Finally, the Yamamoto Behavior Genes project will research the evolution of these genes starting with related Drosophila species. There are over 2400 species of Drosophila and in some groups the species can be traced to a single ancestor. Yet, within these groups there is a wide range of the mating behavior. For example, some species use the lek system while many do not. As traced to a single ancestor, this wide range of behavior is probably due to a relatively small number of mutations. By identifying behavior genes in Drosophila melanogaster, the project will then be able to explore the similarities and differences in the genes which cause the wide range of behavior.

With an increased amount of understanding in behavior genes, it will become reasonable to identify the corresponding genes in higher animals such as mice, or even humans.

## 4) Takai Biotimer (1994-1999)

*Background*

The precise timing of cellular events is crucial. This is well illustrated by the white blood cell's suicidal defense to protect the body against invading bacteria. The presence of bacteria sets off a sequence of events leading ultimately to the white blood cell's death while killing as many bacteria as possible. After it first detects bacteria, the white blood cell migrates to where the concentration of bacteria is highest. It will not waste itself on small numbers of bacteria, so only when the concentration of bacteria reaches a minimum level, will the white blood cell then engulf as many bacteria as it can by a mechanism called phagocytosis. After the cell engulfs the bacteria into vesicles, it injects superoxide into the vesicles to kill the bacteria. At the same time, it secretes proteases into the surrounding medium to kill neighboring bacteria. Finally, the white blood cell dies.

These precisely timed events are set in motion by the attachment of bacteria and bacterial products to the cell surface and the transduction of the resulting signal to various parts of the cell. There are several mechanisms for signal transduction. In the above example, signal transduction for the key events of cell migration, phagocytosis, superoxide formation, and protease secretion involves GTP-binding proteins (G-proteins) which bind GTP and GDP. These proteins are active when binding GTP and inactive when binding GDP. This binding of GTP and GDP appears to be part of a timing mechanism which determines when processes start and their duration.

The example of white blood cells is good for illustrating the various roles of G-proteins. But there are medically and biologically more important processes that involve G-proteins in timing functions. One such process is neurotransmitter release from presynapses with possible relationships to dementia and other memory-related diseases. Another is cell motility of cancer cells and smooth muscle cells with possible relationships to metastasis and arteriosclerosis, respectively. A third is cell proliferation, differentiation, and apoptosis with possible relationships to cancer and embryogenesis. All appear to be related to timing mechanisms involving G-proteins.

*Research Strategy*

The Takai Biotimer project will research the G-proteins and their related proteins, the genes that code for them, and their functions in search for a biological timing mechanism. Research will be divided among three subgroups. One group will research the G-proteins and related proteins, and the genes that code for them. They will clone these genes in order to analyze their structures. A second group will research the expression of these genes and their resulting proteins as they function in white blood cells, in neurotransmitter release from presynapses, and in cell motility, proliferation, differentiation, and apoptosis. The ultimate goal of the project is in the third group which will research the timing mechanisms involving G-proteins and ways in which to control timing by introducing related genes into cells and observing effects on timing mechanisms.

## 5) Yamamoto Quantum Fluctuation (1993-1998)

*Background*

One of the major events of 20th-century physics has been the founding and subsequent evolution of quantum mechanics. At first a strange curiosity that went strongly against intuition

and caused decades of debate that straddled both fundamental physics and philosophy, quantum mechanics eventually became a powerful force in our understanding of the nature of atomic and sub-atomic physics, as wen as a potent tool in the development of new technology.

At the heart of quantum mechanics is the Heisenberg "uncertainty principle", which puts strong limits on quantum systems as well as what can actually be observed: the limits to simultaneously measure both the position and momentum or energy and time. However, according to Yoshihisa Yamamoto, the time has come in which the uncertainty principle can be better understood, and even manipulated as a tool in our development of solid state systems as well as new technologies based on this understanding.

One field where this is especially true is in quantum electronics, where electrons and light are manipulated to make functional devices, such as a semiconductor laser. In this case, light can be confined within a very small cavity. Another such system is a high density of light pulses "squeezed" into very short time duration in optical fibers.

However, although laser light approaches perfection regarding the uniformity of its intensity and the phase coherence, the fundamental laws of quantum physics state that laser light cannot be perfectly uniform in intensity nor in phase. There will always be some fluctuation (noise) in the rates (intensity) and the phases of photon emission. The Heisenberg uncertainty principle of quantum physics states that the product of the intensity noise and the phase noise cannot fall below a minimum value.

Recent research, however, has found that this noise is "malleable": the intensity noise can be reduced if the phase noise is allowed to increase. Likewise, the phase noise can be reduced if the intensity noise is allowed to increase In other words, light can be squeezed. The concept of squeezed light is one result of recent research on semiconductor lasers and optical fibers.

Considering another aspect of quantum mechanics, one myth has held that a quantum system cannot be measured without destroying the system itself. However, more than sixty years ago, a prediction was made that nondestructive measurements are possible under certain conditions. Recent research has confirmed this prediction in the case of measuring of the intensities of solitons in optical fibers. The key is in a trade-off between the measurement err-or in intensity and the back action noise in the phase.

Yamamoto believes that squeezed light and nondestructve measurements are novel results of research on quantum optics, and that as the size of the features in semiconductor devices become smaller, quantum effects become more important. He also advocates that it is now possible to observe the effects of single electrons in semiconductors, and that it will soon be

*Research Strategy*

The Yamamoto Quantum Fluctuation project is pursuing a greater understanding of the uncertainty principle of quantum mechanics while developing much more sophisticated technologies for creating and manipulating electrons and photons within semiconductor cavities.

One part of this research involves the suppression of quantum fluctuations of photons and electrons and the manipulation of electron-photon interactions in semiconductors at the quantum limit. Research includes studying the principles and underlying physics of the artificial manipulation of the photonic quantum state while focusing on the control of spontaneous emission. The artificial manipulation of electron quantum states while emphasizing the quantum fluctuations of electron transport in mesoscopic and macroscopic systems, the suppression of quantum fluctuations and applications to nanostructure devices are also being pursued. Further, control of vacuum field fluctuations and spontaneous emission by semiconductor microcavity

structures is being investigated.

A second theme involves quantum nondestructive (QND) measurements. Techniques using optical soliton and electron interferometry while extending experimental research to wave compression and quantum interferometry are being explored. Efforts include the construction of QND measurement devices, the demonstration of information readout at the quantum limit, and suppression of the free evolution of the quantum system.

Finally, the project is seeking to control the injection of single electrons into mesoscopic semiconductor junctions, and is thus conducting research towards the production and control of single photons emitted from these junctions. Efforts are being made to include an estimation of a micro-pn-junction, the measurement of regulated single electron-hole injection and single photon emission, as well as theoretical analyses of these systems.

## 6) Tanaka Solid Junction (1993-1998)

### *Background*

A major part of human evolution has been ever-expanding technological sophistication. From earliest times the trial-and-error mixing of metals impacted greatly on history. The very same process, but with much greater sophistication, has continued through to the present. Only now, materials are needed to withstand the high stress and temperature during faster and higher flight, to produce better energy efficiency at higher temperatures and to realize faster computing through materials that can rapidly dissipate heat.

A-key factor to succeed in achieving these technologies might well be an understanding of more clever ways to fabricate composite materials which involve a wide variety of shapes and characteristics. A ceramic portion, for instance, could be exposed to high temperature and corrosive conditions that a metal part could not withstand., However, a metal portion could be kept away from the most extreme conditions while providing strength. Some newly developed composite materials have metallic fibers imbedded in a ceramic material to provide reinforcement.

However, the most outstanding aspects of composites and the joining of various materials is the complexity involved. Even for very simple flat interfaces, at the atomic-scale behavior is very complex: dissolving, diffusion, the development of a solid solution and finally precipitation. Other factors that must be contended with are grain boundaries, filler/ matrix, deposited films and brazed joints. Induced stress distribution and lattice defects effect the mechanical properties of an interface. The list goes on.

Although great efforts have been made to better understand the many phenomena involved using electron and other microscopies, the very important interface formation and bonding mechanisms are still little understood on the atomic scale. And although simple-shaped interfaces have been observed, many unobserved complex mechanisms involving multi-step physical and chemical reactions may have led to them. Thus, to further develop the technology of composite materials a much better scientific understanding of the very wide variety of factors involved must be achieved.

### *Research Strategy*

The Tanaka Solid Junction Project is exploring the nature and science of hetero-interface formation from the viewpoints of elementary atom dynamics in and around interfaces while pursuing the possibility of actually designing them.

Concerning interface dynamics, research is pursuing the elementary atomic processes which

occur when solids are joined together, while looking for the nature and controlling factors of hetero-interface formation. How atoms dissolve, diffuse, and otherwise rearrange themselves during an interfacial reaction is being examined. Nucleation/growth theory is also being checked. Both bulky reactions and thin-film deposition are being pursued. The tools being used to facilitate these efforts include high-resolution transmission electron microscopy, scanning tunneling microscopy, and the use of high-energy X-rays. Ways to control an interface using applied stresses and electric and magnetic fields are also being investigated.

Regarding interface properties, an effort is being made to quantitatively understand the various lattice defects and residual stresses which exist around a hetero-interface, which arise during bonding or deposition, and to determine the stress values around interfaces using collimated X-rays along with scanning acoustic microscopy and micro-Raman scattering. Another aim is to characterize any lattice defects induced at or around the interface. Singularities in the interfacial properties are also being investigated with reference to the mechanical, electrical, and thermal properties of their systems. All of the processes around the interfaces must be calculated, including the atmosphere.

Interfaces are also being treated theoretically, using computer calculations to better understand the physical and mechanical natures that exist during bonding or deposition. With a new understanding, attempts will be made to simulate the process of hetero-interface formation, and thereby begin the microscopic design of interfaces. Both simulations and experimental checking will hopefully eventually be carried out simultaneously.

Thus, the main objectives of this project are to find ways to understand both the multi-step functions and physical states at and around interfaces, and eventually to control the interface reactions and properties. The subtitle of this project is therefore the atom dynamics of complex material solutions, since many different materials with many different characteristics and properties must interact. By thoroughly researching the nature and the science of hetero-interface formation, this project will hopefully contribute to the design and fabrication of new materials and components.

## 7) Hashimoto Polymer Phasing (1993-1998)

### *Background*

Nature tends to self-organize towards equilibrium, the driving forces being the tendencies of any system to minimize its energy while maximizing entropy. If one of these forces dominates, simple phase behavior is observed. Entropy favors complete mixing at the molecular level (one-phase behavior); an unfavorable interaction energy favors complete phase separation (two-phase behavior), as when oil floats on water. Even for small molecules, a delicate balance between these two forces can lead to a rich variety of phase behavior on the mesoscopic scale (1 nm - 1 micron); when a detergent is added to oil and water, the oil molecules disperse into the water as mesoscopic spheres, cylinders or even lamellae.

In a similar fashion, most differing polymers separate. Even if one could manipulate them so that they become miscible with each other to form a single phase at a given temperature, there might occur phase separations if the temperature of the system changes. For polymers, the analogous of detergents are block copolymers, chains of two differing polymers that are coupled end-to-end. However, while oil in most cases disperses in water in the form of spheres, the phase behavior of polymer systems containing long-chain block copolymers exhibits a rich variety of different shapes, including cylinders and lamellae; there are also tetrapod networks, meshes and

struts. Of special interest are microphase-separated systems in which the phases form bicontinuous domain structures.

What makes the polymer phase particularly interesting is the dynamics of the phase separation process. Though for small molecules this process is too fast to be observed in detail, for polymers the time scale can be of the order of days. This makes it possible to both observe and control the process. Though it is known that the time evolution involves a non-linear, non-equilibrium process, little is known about the kinds of intermediate structures appearing on the pathway between the one- and two-phase regions.

It has become a significant theoretical challenge to solve the self organization process in these systems and its implications for natural processes, such as those occurring in proteins. Hashimoto believes that if polymers can be used as model systems it might become possible to study these complicated non-equilibrium processes very precisely. He i i also aware that, from a practical point of view, it should be possible to pin the non-equilibrium structures and then use them to create new

*Research Strategy*

The phrase "polymer phasing" was coined to suggest mesoscopic pattern formation via phase transitions and separation in multiphase polymer systems, as a model for complex fluids. Thus, the main research goal of this project is to elucidate basic knowledge concerning the phase transitions in complex fluids, which would allow the design of novel materials by manipulating phase-separated structures formed in the self-organization process.

The first step must be to design and synthesize polymers that self organize on the mesoscopic scale, then watching them on the space-time self-organization process level of multi-component mixtures of these molecules. Unique structures occurring as a consequence of phase transitions are of special interest. High molecular-weight polymers are being heavily used, providing extremely good model systems for understanding non-linear and non-equilibrium problems, because the fundamental length and time scales are large and long. The block copolymers also have interesting features with respect to equilibrium statistical mechanics, forming various phase-separated domain structures; with nanometer periodicity, the so-called nano-patters.

A major theme involves investigating self-organized structures that evolve over wide spatial and temporal ranges, using various space and reciprocal-space methods of structure analysis. The combination of real space analysis by microscopy and reciprocal-space analysis by scattering methods is very important. Although scattering methods are good for analyzing statistical properties and convenient for in situ measurements, it is necessary to understand structural details by microscopy. The dynamical evolution of the self-organized structures are also being studied by both methods and analyzed both theoretically and numerically in order to unveil the laws governing the non-linear and nonequilibrium phenomena.

Another emphasis of the project is to explore methods for controlling the self-organized structures while developing interesting structures having novel properties. This involves the synthesis and characterization of unique monomers and polymers, incorporating isotopic labels, photochromic moieties and other functional groups responsive to electromagnetic fields. These are important both in pinning intermediate structures and investigating structure formation under applied fields. Determining the way in which electromagnetic, stress and other external fields influence the structure is another important aspect of the research being carried out.

Although this project might well uncover new functional semiconductor and bicontinuous structures with combined functionality, its basic aim is to provide fundamental knowledge on the

subtle interplay of the energy and entropy terms that are the basis for their formation and to understand the self-organization process itself.

## 8) Hirihashi Cell-Configuration (1993-1998)

*Background*

The cell is the most basic unit of life. Interestingly, during the course of evolution from single-cell to multi-cell organisms involving many types of specialized cells functioning as an interrelated and holistic whole, both the cell shape and binding among cells have become extremely important regarding the state of the organism.

Setsuo Hirohashi, a pathologist and medical doctor. in the fields of cancer diagnosis and research on the mechanism of carcinogenests, has come to think that the cell shape and binding are interactive elements in what can be considered a "cell society". These elements not only arise from the genetic material found within each individual cell, but are also influenced by contact with surrounding cells and other elements in their environment.

For instance, it has long been known that in certain types of cancers cells lose their shape and become detached from their tissues. They then spread cancer to other tissues, occult metastases, a major factor in limiting the ability of medical science to control cancer by treating only the localized tumors.

Cancer thus provides a window on the cell society, just as a scandal provides a window on the human society that gives rise to it. However, understanding the cell society requires research that goes beyond cancer to examine the society on its own terms. Pathologists are thus constantly concerned with the morphological features of cancer cells, which provide an enormous amount of information. Shape and function and their molecular bases are very closely associated. Cancerous cells have many different sizes: the nucleus is larger and cell polarity is lost.

A very important question is why do cancer cells become disassociated. Recent research has uncovered proteins that bind cells to each other and give cells their shape. Proteins called cadherins bridge the gap between cells. Other proteins called catenins are thought to anchor the cadherins to the cytoskeleton found under the cell surface. For some types of cancer, for example, one of the cadherins is not expressed or mutated and the cells cannot bind to each other. However, if genes for the cadherin are introduced into the cancer cells, the cells can bind to each other.

Hirohashi believes that many molecules involved in the formation and maintenance of cell shape and cell society remain to be discovered. He also believes that the window on cell society provided initially by cancer will open additional windows to provide basic knowledge concerning the architecture and workings of tissues.

*Research Strategy*

The Hirohashi Cell-Configuration Project aims to uncover the architecture and workings of the -cell society. Research is focusing on the shapes of cells as expressions of their genetics and the influences of surrounding cells and inter-cellular environment as well as cell-to-cell interactions. By doing so it might be possible to understand why cells have their particular shapes and functions and why they are built up with particular molecules.

One area of research is concentrating on the genes which are related to shape and binding, while locating, isolating and sequencing them. It is also concentrating on the establishment of in vitro tissue reconstruction models and dynamics, as well as fine morphological image analysis. Further, an effort is being made to understand how these genes give rise to binding and related

functions. To do this, selected genes that are possibly related to tissue formation are being destroyed or reintroduced; the effects on the cell shape and binding are then examined. At the same time, the means by which the genes and functions that they code related to cell shape are being considered, as well as how cell shape is influenced by the surroundings.

An effort is also being made to develop a microscope by which it will hopefully become possible to more closely look at the dynamic changes which take place in cells as well as three-dimensional in vitro reconstituting.

This project is not just concentrating on cancerous cells, but is also very much concerned with the factors that determine the shapes and binding of normal cells. It is also hoped that a system can be established by which it will become easy to determine the mechanism which determines cell shape. If tissue reconstitution can be understood and a means of transferring genes to cells to make their shapes non-cancerous, a sophisticated cancer-treatment method might well be in the making.

## 9) Kawachi Millibioflight (1992-1997)

### *Background*

Every microorganism, plant and its seeds, insect, fish, bird and animal has evolved so as to be critically adapted to the circumstances of its environment. The act of effective and efficient motion in various media is a part of this scheme of nature. Thus every shape and moving mechanism of an organism is closely coordinated with the characteristics of the fluid in which it moves. Yet, the state-of-knowledge today is such that although it is possible to make a rocket-plane like the space shuttle which can blast into space and then glide back to Earth, the aerodynamics of a mosquito, pollen, seeds, or a spider's web are still very little understood.

Interestingly, the hummingbird's flight mechanism is based on the same principle as that of a helicopter or a 350-ton Boeing 747: the phenomenon of lift, utilizing a wing with a rounded leading edge and a sharp trailing edge. Small insects, however, such as the dragonfly, housefly or mosquito, use both lift and drag. Because the ratio of the inertial-to-viscous forces - the Reynolds number - is much different, the fluid dynamics of objects in gaseous and liquid media abruptly change at the millimeter level. The dragonfly, for instance, uses wings that are very thin and rough, which are operated at a low Reynolds number. Other insects are known to fly using additional forces generated by making vortices which remain behind in their wake.

The mathematical foundation of fluid dynamics was stimulated by the desire to design ships, land vehicles and airplanes - human-size objects - so that they could pass through their respective fluids with greater speed and efficiency. However, until now, the movement of organisms has generally been studied by life scientists who often little understood fluid dynamics or stability control. Today, however, interdisciplinary basic research is being aimed at micro-machines and understanding the motions of organisms and objects on scales from millimeter on down.

Since just shrinking big machines to small machines does not work the Kawachi Millibioflight Project is taking a very wide-ranging look at the millimeter-to-nanometer region. In doing so the basic science of fluid dynamics on this scale closely interplays with many fields of science and technology.

### *Research Strategy*

Keiji Kawachi's background includes helicopter rotor-blade aerodynamics using

supercomputers. He has already applied this knowledge to the analysis of hummingbird flight, and is now blending such interdisciplinary fields as biologic mechanics and flow visualization while focusing on situations in which both drag and lift are aerodynamically important.

As a major part of this attempt fluid dynamics is being considered while carefully observing and analyzing the propulsion mechanisms in flying and swimming. To this end, high-speed observational instruments, such as the streak camera, are being developed and used. Wind tunnel and water-tank tests are also being conducted to analyze various models under controlled situations. By these means it should be possible to carefully analyze how the wings, bodies, tails, and other appendages of organisms operate during motion. Interlinking all of the experimental procedures are sophisticated computer simulations.

The biodynamics and control mechanisms of organisms moving through a fluid are also important. For instance, the housefly has vibrating bars on its body which act as gyroscopes to help stabilize flight by providing feedback to the wings. Research in this field involves the various sensory and feedback mechanisms, including wing elastic deformation and beating motions. An effort is also being made to clarify the information systems inside an insect's body, such as the neurons which carry electrical signals, thus helping to develop new types of control systems.

Another important area of this project is bioenergetics. This field involves such questions as how energy consumption is regulated during flight and swimming. The energy supplied by an organism is being compared on a real-time basis with the energy required for propulsion. One important element is to determine how to produce power by using muscle, or the changing rate of gas flow.

Though this is a very basic research project, in today's movement to elucidate and utilize molecular-level processes and machines, any information obtained will surely be valuable. And though this project is starting out by analyzing organisms on the millimeter level, it could well set its sights at the level of bacteria and smaller, where the fluid dynamics involve situations on the scale of the mean free path of molecules, and are almost completely different and unknown.

## 10) Itaya Electrochemistry (1992-1997)

### *Background*

In a physical universe comprising the solid, liquid, gaseous and plasma states of matter, it is natural that many important phenomena ,take place at the interfaces of these states. Concerning the inter-faces .between solids and liquids, some very common examples include the -corrosion of metals, the charging and discharging of a storage battery, and the wet processing of semiconductor devices. Many such processes involve electrochemical oxidation-reduction reactions.

Although these and related phenomena have long been stud-led, until recently knowledge concerning the atomic and molecular processes that occurred at the interfaces have depended on indirect experiments. One of the major reasons for this is that there has been no good observational technique that could work in a liquid. Thus, most previous information results from observations made in high vacuum after removing a solid sample from liquid. During this process irreversible reactions, such as surface oxidation and contamination, often occur, thus complicating the analysis of surface structure.

Recently, however, techniques involving scanning tunneling microscopy (STM) and atomic force microscope (AFM) have been extended observations of solid samples immersed in liquids, thus allowing direct observation of the solid/liquid interface in its reacting state. On of the most

important advancements in this field is a system called electrochemical STM developed by Kingo Itaya. In this system having a four electrode configuration, the electrode potentials of the substrate and the tip can be independently controlled relative to a reference electrode. This apparatus thus offers new possibilities for complete in situ observation of electrochemical reactions under potentiostatic conditions, since the. can be continuously scanned over a surface, even while electrochemical reactions are occurring at the working electrode.

The Itaya Electrochemiscopy Project is using these new techniques examine electrochemistry at the atomic and molecular levels. project is treating the solid/liquid interface as a reaction site in order to uncover the mechanisms of surface reactions while pursuing, the precise control of these reactions. Analysis is focusing particularly on the reactivity and structure of solid surfaces in the presence of adsorbed and solvent layers.

*Research Strategy*

In order to understand interface structure an effort is being made to establish methods to form well-defined solid/liquid interfaces. This is being done by using many types of single-crystal surfaces along with both aqueous and nonaqueous solvents. Research is also focusing on new ways to make measurements and to control surfaces using in situ scanning probe microscopes, such as STM and AFM. In addition, the use of ultrahigh-vacuum surface-analysis techniques is being pursued. As part of this pursuit, special multi-chamber vacuum systems are being developed in which solid samples can be removed from a liquid and then analyzed without experiencing oxidation or contamination.

Regarding interface formation, work is concentrating on the bond formation reactions which occur at the solid/liquid interface. For example, the mechanisms by which metal and semiconductor surfaces are electrochemically formed and dissolved, thin-film crystal growth processes, as well as the adsorption and orientation of ions and molecules are being pursued. In addition, the formation of modified surfaces and new methods for making thin films using knowledge gained about reactions at the solid/liquid interface is being studied.

Another area of concentration concerns interface fabrication, while concentrating on reactions that break bonds at the solid/liquid interface. The processes involved in chemical and electrochemical etching as well as in dissolving adsorbed molecular layers should hopefully be clarified. To this end, the electrochemical energy and optical energy necessary to control reactions at the solid/liquid interface are being applied. A search for technology to control metal and semiconductor surfaces at the atomic and molecular levels is also being conducted.

## 11) Yanagida Biomotron (1992-1997)

*Background*

One of the great mysteries of science is how such a large organism as the human being with billions of individual cells and their sub-components can move with smoothness and energy efficiency as a unified whole. And it does this regardless of the speed of action or the forces involved. These characteristics exist all the way from the large-scale whole to the sub-cellular.

The heart of most investigations on muscle contraction has been within the muscle cell. There, huge numbers of nanometer-size biomotors - called biomotrons - are involved in the most basic aspect of motion. Each biomotron is a complex formed by the act of a myosin protein head attaching to, and by pulling on, a 7-nanometer thick action filament. Biomotrons convert chemical energy into mechanical kinetic energy with up to 90% efficiency; and they operate with little

friction while adapting to their circumstances, even by easily aggregating to form large muscle systems.

The flexibility and efficiency of the biomotron stands in sharp contrast to the situation of man-made machines, in which efficiency requires high-rigidity and -energy inputs to overcome interfering thermal vibration. Precession requires large external frames to hold the parts in alignment. The biomotron operates without these requirements due to unknown principles of engineering.

Recent seminal research carried out by Toshio Yanagida on biomotrons is consistent with the existence of such unknown principles, such as that involved in energy transduction and action. The former common wisdom was that a single attach-move-detach cycle of the myosin-actin complex in a biomotron is accompanied by the hydrolysis of one ATP molecule. In reality, the biomotron can spread the released energy across several attach-move-detach cycles.

Another interesting aspect is that compared to a man-made chip, for instance, the biomotor needs no special isolation from the environments to maintain good communication, even at a very low signal-to-noise ration. Further, a huge number of biomotrons can exist within a cell and operate efficiently at body temperature. The molecular motor therefore seems to be very skillful at communicating within its network. It is thus becoming clear that a considerable degree of control occurs within the biomotron without direct control by the higher nervous system. In this sense the elements of the molecular machine have "intelligence" to sense what is happening around it.

Yanagida never liked the standard model of muscle operation, since it was too similar to the operation of man-made machines. The Yanagida Biomatron Project thus aims to uncover the uniquely biological operations and structure of the biomotron.

***Research Strategy***

The traditional method to observe biomotors is to stain them within cells with a fluorescent material. Optical microscopy reveals their motions and interrelationships. The actin is usually bound to a glass surface where ATP energy is added. To increase the dynamic observational capability in a liquid medium various instrumentation having nanometer resolution and a millisecond time scale is being sought, such as evanescent laser optics (PSTM) as well as STM and AFM in high speed imaging and low-level light detection.

Yanagida has already developed a delicate technique in which a specially coated glass micro-needle is manipulated by a piezoactuactor to catch and attach to an actin filament fixed to a glass surface. In this procedure both the nanometer movement and pico-Newton force involved in the actin-myosin molecular-motor reaction can be measured on a 0.1 millisecond time scale while being observed in a liquid medium by fluorescent optical microscopy.

Instrumentation is also being developed for real-time tracking and measuring of the chemical reactions which occur in biomotrons in order to formulate chemical-kinetic energy transduction theories concerning, how the biomotors run so efficiently and under ambient noise conditions and under varying loads. Since during one ATP interaction this motor produces many impulses, not just one, an important question is how a biomotron can control the rate of chemical energy release.

Structural analysis, which involves both the static and dynamic structures of the proteins that make up a biomotron is also being carried out. The interface and interactions between molecules are being studied as well as how the molecular-level actions of biomotrons are translated into macroscopic motions.

Since it is impossible to connect each biomotron individually to the brain by a neuron, a

systems analysis of the higher-level motion systems from many biomotrons is being analyzed. Interacting biomotrons and the interfaces between the parts of biomotrons are also being studied, as well as reconstituted systems and intermolecular cooperation and information transmission in these systems.

## 12) Yoshizato MorphoMatrix (1992-1997)

*Background*

One of the most intriguing questions in biology is how starting from a single microscopic cell a macroscopic entity comprising billions of cells and having complex functions and shape that far transcend the characteristics of the original cell can grow through repeated division and differentiation. And all of this is done based on a single set of rules existing in the DNA of the original fertilized eggs Further, throughout its life each organism can heal injuries, and in some cases, such as frogs, can even undergo dramatic transformations, called metamorphosis

Although much is known about the biomolecular mechanisms by which cells divide and differentiate, the processes by which they arrange themselves to give the body shape and wholeness are little understood. Perhaps this situation exists because most previous research focused on cells rather than what is called the extra cellular matrix (ECM). In plants the ECM is the wood which binds the plant's cells. In animals, it comprises a complex combination of several kinds of proteins including at least 13 types of collagen as well as laminin, fibronectin, and proteoglycans. The proteoglycans can also hold other control molecules, such as growth factors and hormones.

Normal animal cells require some substance to which to adhere; otherwise, they cannot express normal functions. Connecting is just one function of the ECM. Another important function is to provide locations for adhesion. When ECM components and cells are mixed they recognize each other, and can thus combine together to self-organize tissues and organs. The orientation of cells is also an important phenomenon. possibility is that orientation occurs when one cell adheres to the and the cell membrane becomes polarized. This type of difference it cell surface is also important for expressing normal function and specific form.

Katsutoshi Yoshizato believes that one of the most important ingredients for understanding the ECM, its components, and related metamorphosis is to take a very eclectic view. Just as looking at only cell biochemistry has failed to reveal the strategy for making a whole organism, anything but taking a wide view of all of the factors involved is insufficient. It is the overall picture - the cells in combination with the ECM - that is important.

*Research Strategy*

The Yoshizato MorphoMatrix project is seeking to uncover the mechanisms for higher order organization and structure formation in animals by taking regeneration and transformation as the reconstituting of animal bodies and researching the role of the ECM in them. This project is a biological version of chemical self-organization: the self-organization of biological polymers and cells.

A major theme in this project is to observe the regeneration and transformation mechanisms of organism. Emphasis is being placed on the frog and newt due to their outstanding regenerative and metamorphic abilities. Research includes investigating the molecular mechanisms which determine transformations in the head and tail regions, while focusing on the expression of homeotic genes as well as the genes for ECM molecules. Thus, the regeneration mechanism of the

tail region, as influenced by thyroid hormones and retinoic acid, should be elucidated. In addition, the chemical entity of the mesenchymal factor which determines the region-specific differentiation of epidermal cells is being studied as well as the role of the ECM as a structural information molecule with controls regeneration and transformation.

The bearer of information for regeneration of tissues and organs in response to injury, and the factor which controls structural transformation is either ECM, itself, or something closely related to it is being studied. By clarifying this factor, it should become possible to investigate the role of ECM as a structure-information molecule as well as the mechanism by which signals from ECM are transferred into genes.

Using the cells and ECM which participate in the regeneration and transformation of tissues and organs, a search is being made for ways to reconstitute in-vitro the three-dimensional structure of tissues and organs. In order to construct an artificial model of this process, a search is being made for ways to analyze and reconstitute higher order structures (tissues and organs) by using the self-organizing properties of cells and biological polymers.

In addition to developing basic concepts related to the formation of structure in animals, this project is expected to provide the basic advances which will contribute to medical technology in the areas of artificial organs, such as tissue, transplantation and the treatment of trauma.

## 13) Yoshimura pi-Electron Materials (1991-1996)

*Background*

All of nature's plants, animals and minerals contain molecules with two kinds of electron orbits: sigma and pi. The sigma electron structure holds nature together, providing strength. The pi-electron structure, comprising clouds extending normal to the bond axis between atoms, allows electrons to be mobile, resulting in bright green and red coloration, as well as the absorption of the light necessary for photosynthesis.

Although the pi-electron cloud is a fundamental reaction field for organic and biological materials, such as photo charge-transfer reactions, the pi-electrons in these compounds cannot migrate freely without running into "barriers". In contrast, delocalized pi-electrons can move widely throughout an inorganic crystal or molecule - graphite, for example - without distorting it. Such materials comprising them thus have many interesting characteristics, including low effective mass, extremely high electron mobility and superpolarization - n-electrons migrating over long distances when placed in electric fields.

Susumu Yoshimura, while being a group leader in the Ogata fine polymer ERATO project, discovered how to make graphite materials that are large single crystals - called 'super graphite" - while studying the electrical properties of organic polymers. The electrons in graphite can move faster than the electrons in gallium arsenide HEMT (high electron mobility transistors) that are being developed for the newest generation of supercomputers. Under the right conditions they may even become superconducting.

Little is known, however, about the roles of n-electrons in solid surface states or the quantum effects in two-dimensional conductors. Typical n-electron materials are low-dimensional graphite made in the forms of fibers and blocks having physical properties almost identical to those of single crystals. Carbon clusters, such as C60 and C70 -Bucky balls - can now be processed in large quantity. Although the probably not a form of graphite, they can be made from graphite, an supergraphite materials are a good starting point for studying them.

*Research Strategy*

This project aims to study the large space occupied by freely moving pi-electrons as domains of electron motion and material transformation while elucidating the unique physical, chemical, and biological phenomena while result from these domains. In order to achieve these goals synthetic methods are being developed for new materials with extended pi-electron systems, and showing high crystallinity. The mechanisms of superpolarization, high electron mobility and nonlinear phenomena are also being elucidated while studying chemical reactions and electronic functions.

One part of this project is to create new synthetic methods for both organic and inorganic pi-electron materials. In 1-dimensional graphite, for example, benzene rings can be made to extend in only one direction, whereas ordinary graphite has benzene rings in two dimensions. Carbon clusters which contain benzene rings, or pi-electrons condensed in a cluster, are also being sought.

Chemical and biological reactions are being designed on the surfaces of pi-electron materials, such as graphite, Bucky balls and silicon. There is much interest in the biological activities made available by pi-electrons, such as proliferation or mutation. If there is a sudden change in the form of the character of a biological cells, as a basic property or structure, it probably involves some reaction involving pi-electrons.

Graphite can be synthesized at very low temperatures (200 deg C, rather than the usual 3000 deg C) by controlling the structural order of the starting materials. In making graphite to be incorporated in semiconductor devices, low-temperature preparation is much more convenient. Further, the electronics states of n-electron materials are being studied using various equipment, such as the STM. More understanding should allow basic concepts to be developed for devices based on graphite and other pi-electron materials.

Material science based on pi-electrons should enrich our knowledge concerning the optical, electronic, magnetic, chemical and biological, properties of n-electron materials, leading to new higher speed electron devices. Superpolarizability may lead to new nonlinear - red light in, blue light out - optical devices, which are essential for computers based on light. Biocompatibility might allow new materials for fabricating artificial organs. Bioactivity might result in new stocks or mutants.

## 14) Noyori Molecular Catalysis (1991-1996)

*Background*

A perfect chemical reaction would produce only the desired product, with no waste f either raw material or energy. This would allow chemists of exactly the desired shape, including chirality.

Ryoji Noyori's research interests have been primarily in the exploitation of new synthetic methodologies - particularly those based on organometallic chemistry - and their applications. In 1966 he reported the first example of a homogeneous asymmetric reaction catalyzed by a transition-metal complex; in 1991 he received the prestigious John Gamble Kirkwood Award for his work in asymmetric synthesis and catalysis. He also developed many practical catalysts for a wide variety of asymmetric transformation, with optical yields of over 90%, or even close to 100%, frequently being obtained.

Noyori's strategy involves synthesizing well-shaped organic compounds, then attaching them to a central metal; it is thus possible to control the reactivity of the central metal through such a coordination of the organic ligand. Particularly important is regulation of the stereochemical

outcome of the reaction, especially differentiation of right and left handedness. This technique must play a key role in science and technology at the molecular structural level.

In certain cases, the efficiency of artificial metal complexes rivals that of natural enzymes, allowing the production of large amount of chiral compounds having both natural configurations with the use of only a very small amount of chiral source. Some of them are applied to commercial production of significant compounds of external high enantionmeric purity. Until 15 - 20 years ago, the major way to obtain optically active compounds was resolution, because many synthetic chemicals are a 50/50 mixture of right- and left-handed molecules.

Noyori is particularly noted for his initiation of BINAP-tra metal chemistry (BINAP = phosphorus-based chiral organic ligand) which opened the tremendous potential to synthetic chemistry. His original research concerning homogeneous catalysis contributed to the development of an industrial process yielding (-)-menthol, a very useful fragrance. The industrial process of beta-lactam antibiotics, a penicillin analogue, using Noyon!s asymmetric hydrogenation technique, has just started.

*Research Strategy*

The Noyori molecular catalysis project will utilize a modem organometallic strategy. The basic principle, "molecular catalysis," relies on 4-dimensional chemistry in which high efficiency is only attainable through a combination of both the ideal 3-dimensions (x,y,z) and appropriate kinetics (time). Well-designed metal complexes possessing chiral organic molecules as ligands are used not only to accelerate repeated chemical reactions, but also to precisely control the stereochemical outcome in a desired manner. Thanks to the diverse reactivities of the central metal atoms or ions, as well as unlimited structural permutability of organic ligands, this chemistry presents a general principle for the multiplication of chirality. "From ready-made to tailor-made catalysts" is a major theme of the project.

This project is focusing mainly on efficient reactions which can make both right- and left-handed molecules, either large or small, with high enentiometric purity. The project is also examining catalysts for the synthesis of stereo-regular polymers in which all of the chains are the same length. Catalysts with molecular exactness which approach perfection in catalyzing reactions that nature cannot perform are being studied.

Even though the design of catalysts is still empirical, the computer can be used to make models of chemical reactions. Strong emphasis is also being placed m the efficient synthesis of bioactive compounds. Important in biological science is the fact that many sites interact with molecules through molecular recognition, where matching of chirality plays a key role.

Further, high purity at the molecular level provides a new power to create new functions and materials. A typical example is liquid crystals. Many compounds and advanced materials (optics, magnetics, and electronics) need some appropriate molecular assembly, requiring a strict matching of chirality. Very pure, optically active compounds can make nice molecular assemblies. This will be the most important theme required to make advanced materials.

A strictly controlled synthesis of polymers having the same molecular weight and stereochemistry should provide a very powerful tool, particularly in the area of material science. The bulk properties of macromolecules, either natural or artificial, which are highly stereo-regulated in an absolute sense, are very different from those of stereo-random polymers. Synthetic polymers, which can not be produced in nature by enzymic reactions, which are purely left-handed or right-handed, may lead to unique, advanced materials. Since the evaluation of new polymers is very important, work in this field is also being carried out.

## 15) Fusetani Biofouling (1991-1996)

*Background*

To the many existing species of biological organisms evolution has provided sophisticated chemical systems for communications. These are used for internal regulation, communication among members of the same species and protection from lethal, competing species. Such systems are found not only among terrestrial organisms, but more copiously among marine plants and animals. Regarding sea organisms - such as sponges, corals, mussels, barnacles, and tunicates - very little is known in this relatively young field, which started in the 1970s. This is partly due to the fact that research has been fairly scattered among disciplines as well as target species. Further, whereas plants can be touched and observed directly, sea organisms are much more remote.

A barnacle larva upon hatching from its eggs several times and swims for a while before automatically embarking on a "search" for a place to settle and grow. Carried by ocean currents, it floats and swims, while bumping into rocks, plants, fish, and a multitude of other organisms that influence each other while living in far higher densities than those found on land. Organisms already growing in some ecological niche have chemical control mechanisms for preventing the settling of other, competing larvae. Eventually, the larva comes into contact with unique chemical signals that indicate a satisfactory location for its particular species. The larva soon binds tightly to its new ecological niche and begins to make its shell and grow.

The biofouling process includes a very wide variety of phenomena, from the settlement and metamorphosis of marine organisms within their natural habitat, to chemical communication among organisms and defense. It also involves the pathways and decisions that facilitate these functions. Once a larva touches the right place and receives a signal to stop and grow, many processes take place. Transmissions. within the organism of information provided by these chemical substances can be understood to be due to the binding of chemical signals to receptors and the subsequent action of secondary messengers, similar to nerve transmitters and hormones. This project has some similarities with two other ERATO projects, the Mizutani plant ecochemicals project and the Torii nutrient-stasis project, since the communications systems of animals and plants on land or in the ocean might be quite similar.

*Research Strategy*

The Fusetani biofouling project is studying how marine larvae know when and how to stop, attach, and grow, while paying special attention to barnacles, mussels, hydroids, and bryozoans. In order to understand settling it is not only necessary to search for the chemical substances involved, but to carry out broad investigations of the structure, function, and characteristics of the receptors, as well as the functions of secondary messengers.

Although the biggest challenge of this project is to learn how to test chemical signals and settling in the laboratory, even before this is done the isolation and characterization of possible signal chemicals are being pursued while researching for a basic physiology of larvae in order to determine what pathways exist for signal flow. Once this is achieved attempts will be made to determine the chemical signals that trigger the settling and transmission and changes that larvae, while describing the signal transmission and changes that occur within the larvae.

More specifically, the project is searching for settlement-promoting and -inhibiting compounds using highly sensitive bioassays, such as the electrophysiological type. It is also studying the characteristics, structure, as well as distribution of receptors and the expression of

function by secondary messengers in order to determine the roles of chemical signals in settlement. Attempts are being made to attach microelectrode probes to the antenna, or receptors, of the afore-mentioned organisms in order to pick up actual signals, and to understand the many neurotransmitters, which may act directly on the nervous system.

This research should not only contribute to our understanding of various life forms in the ocean, but should also provide basic knowledge which can be applied to protecting marine environment and culture. From this research better ways might be found for controlling harmful marine organisms, thus helping to solve problems that have plagued humans for millennia, such as barnacle growth on ships, fishing facilities, as well as a wide variety of other man-made objects in the oceans. Better ways to cultivate oysters, abalone and other marine organisms for food might also be found, while, perhaps, also producing valuable

## 16) Okayama Cell Switching (1991-1996)

*Background*

The various parts of an organism are formed by cells differentiating into new cells which provide specialized functions. The cells higher life forms - yeast, plants and animals - grow and divide in a repeating four-step cycle: dividing; growing (Gl); copying their gene and growing more (G2). Because this process is crucial, the simple cycle has been left almost untouched by the ravages of time and evolution: for instance, the genes that control- growth in human cells also function if put into yeast.

G1 growth immediately after division is the most crucial time, since some uncertainty exists if the cell win actually copy its genes; divide; produce sperm and egg cells; change form; or lose control, becoming cancer. The cell's fate is determined by events which occur during G1. Thus, a cell's aging or becoming cancer can be considered to be a type of differentiation. Approaching cell switching based on gene expression and control may uncover a mater switch deeply related to the existence of living organisms.

*Research Strategy*

This very basic project is utilizing a wide array of recently developed tools in order to unravel the secrets of G1 and how to regulate it. Although each human cell contains more than 100,000 genes, only a fraction has been identified regarding structure and function. Very little is known - such as where or how far apart - about the genes that are involved in actually controlling cell switching.

One tool for understanding the Gl process is a specially designed gene library containing DNA cloned from cells, perhaps human, muscles. In the millions of volumes there may be many duplicates as well as missing "pages" or "chapters". This library also contains genes engineered to function in a wide variety of cells, from yeast to human, in order to search these libraries for the genes that control Gl.

One search is being carried out with fission yeast mutants which have Gl defects. Efforts are being made to locate the human gene that corrects this defect. If it can be decoded - determine the structure of the protein that is made from it - from the protein's structure clues can be found as to its role in Gl. To express mammalian, even human, genes in yeast, simply cutting out the gene and putting it into yeast doesn't work.

This is because the gene structure, especially the promoter, is different. However, since the protein coding region is quite similar, it can be expressed in yeast. To do this, a promoter must

be provided which works in yeast, necessitating the construction of some special construction vector. After making a cDNA library and putting all of the cDNA into this vector, a cDNA library will exist which can be introduced to yeast. Any yeast cell that acquires the gene corresponding to the defective gene is cured and can grow, the basic concept for selecting human counterparts.

By investigating the functions of individual genes and the mutual interactions of gene functions, it should be possible to uncover the control mechanisms for gene clusters. By introducing and substituting genes, a mammalian master switch can be constructed in yeast which can be used to explore ways to artificially control differentiation.

Another search is being carried out using a special kind of rat kidney cell: it becomes cancerous if exposed to growth factors. If the growth factors are taken away, the cancer stops and the cell returns to normal. The cancer can thus be turned on and off. Several mutants have this rat kidney cell, from which it has been learned that there are switches in Gl. A search of the human gene library for genes that can correct the defects in these rat cell mutants is being made. Using these genes, it should be possible to learn about switches that turn on cancer in humans - and, perhaps, clues as to how to turn them off.

Efforts are also being made to reconstitute the control system, particularly the mammalian control system, in yeast. To artificially control this cell switching at a given organism is being pursued. Information concerning the universal control mechanisms for cell propagation and differentiation win hopefully yield clues to molecular mechanisms of cell aging, immortality, and oncogenesis.

## 17) Kimura Metamelt (1990-1995)

### *Background*

Even though many man-made products are solids which evolve from melts - glass, steel, aluminum, copper wire, plastics, and semiconductors - very little is presently understood about the processes involved. Sometimes literature data vary by an order of magnitude, a situation that is very different to that regarding solid state materials. Researchers are therefore searching for a clearer vision of the details concerning the many physical changes that take place during a melt which critically effect the final product.

Since the densities and inter-atomic distances of a melt are close to those of a solid, the attraction between molecules is much stronger than in a gas, suggesting that there must be some form of structure. Shigeyuki Kimura is a crystal grower who has experienced more than a few anomalies over the years regarding the melt process, and has come to believe that nanometer-size clusters comprising several hundred atoms with some sort of microscopic structure are continuously moving while changing position with respect to each other. The Metamelt Project is attempting to elucidate the very basic mechanisms - "equilibration processes" - concerning the dynamics and processes of melts.

### *Research Strategy*

This project is focusing on the changes which occur in melts over time, while analyzing them regarding both structure and behavior. Of special interest are the melts of silicon.

As a key investigative tool, the possibility of using high-intensity x-ray beams to obtain scattering and small-angle diffraction of liquid melts is being explored. Another technique that is being developed involves nonlinear laser spectroscopy. These and other techniques are being used to study such relaxation phenomena as viscosity, density, surface tension, and thermal diffusive

characteristics. Direct observations of flow patterns in melts combined with simultaneous computer modeling are also being carried out.

An increased understanding of the microstructure and ordering melts should lead to new materials and new processing technology. It is also hoped that the information gained through this project will allow crystals to be "grown in a computer" before actually carrying out production, as is done in the creation of large integrated circuits. This would allow custom designed optimum furnaces and growth conditions.

*Research Progress*

o In a study of how impurities behave in the molten state with silicon, antimony was investigated, since it is often used in high concentrations. By using a computerized investigative technique based on a combination of solubility and evaporation measurements it was found that antimony interacts with oxygen produced by the Czochralski crystal-formation process to form $Sb_2O$ molecules, a very unexpected and unique results. This new method is now being used to investigate other impurities in silicon. By using this technique it has become possible to predict what is going on at the interface of the molten and crystalline states, a point of long-time interest.

o Opposed to the common wisdom, it has been found that the density of a silicon melt as a function of temperature is not linear. A series of tests using various unique techniques has shown that there are at least three specific regions. In each region there is a different thermal coefficient, one of the most important factors when making a computer simulation. If it is high the tendency for convective currents is also high.

o It has been believed that a molten material once melted does not change. However, it has been shown that changes continued to take place even after 500 minutes. This study is being extended to longer time intervals. Such information is important regarding the final characteristics and quality of a crystalline material after being produced through a melt.

o When employing the Czochralski method for crystal formation a standard procedure is to use the rotation speed to control the amount of oxygen impurity in the crystal, believing that oxygen from the sides of the $SiO_2$ crucible is increased with rotation speed due to friction and other factors. However, both experiments using X-rays and tracer comprising tungsten coated with carbon as well as simulations have shown that increased rotation speed causes the oxygen to evaporate from the surface after complex circulation patterns, though oxygen coming from the bottom of the crucible does enter the crystal with increasing rotation speed.

o A new X-ray energy-dispersive analysis technique has been developed by which the situation surrounding individual atoms in a melt as a function of the temperature and other factors can be determined for the first time. The change as a function of temperature is believed to be related to the (above-mentioned) finding that the density is a non-linear function of the temperature.

**18) Nagayama Protein Array (1990-1995)**

*Background*

Life in the universe as we know is based upon systems of cells: bacteria to trillions of complex interacting cells -an is sometimes instructive to consider these cellular units as containing various molecular machines consuming while carrying out complex processes and manufacturing new materials. Interestingly, many of the components of cells to proteins to protein complexes (supramolecules) to cellular formed by self-assembly under the instructions of DNA. These cells

also produce all of the proteins and supramolecules necessary and ultimately organisms that are a million-times original simple protein.

If human are to connect the manufacturing carried out at the bottom level of life with their future technology it will be necessary to both understand and harness the self-assembly abilities of protein molecules - mesoscopic hands for human use. Until recently it has been generally believed that proteins are structurally weak, and thus unsuitable to join silicon, gallium arsenide and the other materials that form the backbone of human technology. Kuniaki Nagayama, however believes that proteins are far tougher than ever imagined and that once their self-assembly abilities are understood and co-opted, much interesting and natural technology will become available.

*Research Strategy*

The Nagayama protein array project is dedicated to finding techniques by which proteins can be coerced to self-assemble into a wide variety of 2D assemblies with unique features. To achieve this goal, not only do the protein-protein interactions and self-assembling processes need to be elucidated, but suitable substrates, or fields of space, must be perfected. Rather than using biomembranes, like those found in nature, an attempt is being made to utilize mobile fluid layers made on very clean substrate surfaces.

Six years ago Nagayama developed a technique to spread proteins on mercury, which provides a very clean, flat surface. The present project is now generalizing this concept. It is also developing techniques by which assembled protein crystalline films can be transferred to the surface of ,a carbon or other substrate in such a way that the ordering of protein crystals can be preserved.

Further, an attempt is being made to maintain the original function of proteins while controlling their manner of integration on a substrate
surface. By doing this it might be possible to design protein arrays
having critical catalytic sites at optimum positions and orientations on the surface. To prepare a protein array with such desired 2D patterns, the properties of protein-protein interactions are being changed by chemically modifying and genetically mutating amino acids on the protein surface and reshuffling domains using genetic engineering.

*Research Progress*

o The nucleation process in the assembly of proteins has been theoretically and numerically analyzed, and the local structural changes associated with mutagenesis calculated. Also, the surface charge contribution in relation to the effect of the surrounding ionic strength of the crystal stability has been investigated for ferritin using dielectric models. Hexagonal and squarely packed ferritin arrays have been prepared by controlling the inter-molecular attractive forces. Transmission, scanning electron and atomic force microscopes were used to define the structures.

o The dynamics of the 2D array formation of latex particles have been observed on a solid substrate by means of optical microscopy. The observations suggest a two-stage mechanism of 2D crystallization of small particles: 1) nucleus formation, governed by attractive capillary forces appearing between particles partially immersed in a liquid layer; 2) crystal growth through convective particle flux caused by water evaporation from the already ordered array. This is a very general technique which can be applied to a wide variety of fine particles, including proteins. The new term "convective assembly" has been coined to describe this self-assembling crystallization process.

o Many recombinant proteins with modified surfaces have been made using genetic engineering. Convective assemblies prefer to use large and globular protein elements in the assembling process. By taking this as a "golden rule", large structural "artificial supramolecules" are being designed and made from the recombinant proteins, and then assembled. The structural sophistication is in accord with the strategy used by Nature, "biological hierarchy,". In these attempts, however, an attempt is also being made to employ carbohydrate engineering, and even organic chemistry, as well as genetic engineering.

o It has been found that fluorinated oil (used as artificial blood), having twice the density of water, is an excellent fluid subphase upon which a 2D protein can be made. Further, being quite volatile, it quickly evaporates, allowing the array to naturally lower onto a solid-surface substrate. It has r been found that even an aqueous solution, when it has a higher density than nominal water, can be used as a flat subphase.

## 19) Torii Nutrient-Stasis

*Background*

Even though nutrition and its biological mechanisms are extremely important, these subjects have not generally been a part of mainstream basic science. It was only recently that both scientists and the medical profession have come to realize that not only do the quality and quantity of food intake play a wide variety of critical roles in the health of any animal, but so do the condition of the internal mechanisms that regulate nutritional desire, biochemically as well as physiologically.

Along with a growing understanding of DNA, it has been learned that many times those susceptible to such diseases as hypertension have some accumulation of genetic defects. One type causes an extreme desire for salt, leading to hypertension. Many other diseases probably result from breakdowns at the basic level of the DNA and/or parts of the complex physiological systems that constantly monitor and regulate nutrition and metabolism.

Kunio Torii has long been concerned with what he calls "nutrientstasis" - the ability of animals to subconsciously seek out those nutrients which are necessary for good health, but are missing in their diet. In this process the animal's cellular, especially neural, metabolism is continuously changing in an attempt to maintain an optimum balance internally available nutrients.

*Research Strategy*

The Torii nutrient-stasis project is studying the mechanisms by which animals change their diet in response to changes which occur both externally and internally. To this end, diets with varying degrees of nutrient balance are provided to animals while being observed externally by video and automatic monitoring of feeding devices. Internally, they are observed by monitoring body fluids in the alimentary canals, blood vessels, and brain, which indicate changes in hormone levels and growth factors.

Another important aspect of this project is to define the brain's "nutritional headquarters". To this end, magnetic resonance spectroscopy and imaging (MRSI) is being carried out. By performing brain and organ scanning it is possible to observe such chemical activity as the metabolism of animals after being fed various diets. It is hoped that these observations will allow a categorization of ATP use and how animals choose food. An outline of the chronology of the regulatory system before and after meals is also being pursued.

Further, by inserting very small probes into the critical regions of the brain related to

nutritional behavior and metabolism, it is possible to continuously record the brain function in each neuron of a particular area without the use of anesthesia. Hormones and growth factors, including neurotrophic factors, are being applied directly to selected parts of the brain while following changes in both the feeding behavior and metabolism. In other experiments the desires of animals suffering from such metabolic diseases as diabetes, senile dementia as well as renal and hepatic failure are being continuously observed while isolated from external contamination.

The composite knowledge gained from this research will hopefully give a better understanding of the basic biochemistry and physiology by which animals maintain themselves through diet. This information might well lead to the prevention of metabolic failure in humans with the advance of age as well as
other nutrition-related diseases, while providing heightened health.

*Research Progress*

o An operant behavioral test system was developed by which the behavior of rats fed a nutrient-deficient diet can be analyzed. Specifically, rats which were fed an L-lysin (Lys)deficient diet selected a Lys solution over a variety of others. Further, direct infusion of Lys into the lateral hypothalamic area of the brain removed the desire of the rat to select this nutrient, but did not for the other amino acids. Thus, neuroplasticity in the hypothalamic area was established. Also, it was found that information seems to travel from the oblongata to the hypothalamus and that the brain cortex integrates information between the hypothalamus and other areas.

o Possible neurotrophic factors in serum from rats with and without deficiency of either protein or Lys were assayed. An increase in serum inhibin and activin A was observed in rats fed Lys-sufficient and nonprotein diets, respectively. However, serum activin A-like activity was severely suppressed under Lys deficiency. Further, immunohist6chemi'a] distribution of activin A in the brain was observed in addition to the finding that Lys-deficient and nonprotein diet caused a change in the serum levels of activin A as a possible neurotrophic factor. This release may elicit plasticity in the sensitivity for deficient amino acids of neurons in the brain nuclei that could selectively drive ingestive behavior for particular amino acids to maintain amino acid homeostasis.

o An exceptional MRI analysis system has been developed as a sophisticated observational tool. Its characteristics include a 4.7 tesla magnet with a bore size of 40 cm., providing a large (sufficient for a monkey's head) and stable magnetic field in the bore. Further, the computer systems have been improved and new probes involving copper and plastic wires and tubes developed, which should allow for discrete imaging of neural activity in specific brain regions in response to changes of nutrient status.

## 20) Shinkai Chemirecognics (1990-1995)

*Background*

In any organism millions of biochemical reactions are continuously taking place. Many of these occur due to very specific lock and key interactions oxygen carried in a special receptor site of hemoglobin cells held together by inter-cell proteins; enzymes that stimulate highly efficient, specific reactions; antigen-antibody interactions which accurately distinguish targets.

One of the most interesting species of molecules which undergoes host guest type specific relationships has a ring shaped structure. The first such inclusion compound known was cylodexterin, which has the ability to recognize and bind to organic molecules. The second comprised the crown ethers: hydrocarbons and oxygen which electolytically bind to various guest

metal ions, depending on the sized of a fairly flexible ring.

Even more interesting is calixarene. Since its is in the shape of a bowl -"calix" means crater rather than a simple ring, it can interact with guest molecules in a much more specific and strong way. The work "arene" indicates aromatic compounds like benzene. According to Seiji Shinkai, these molecules are especially useful as hosts to metal cations and organic molecules. The do this through the intricate combination of hydrogen bonds, coordinating bond, hydrophobic bonds, electrostatic interactions, CT-pi interactions and others.

Through various possible simultaneous interactions well as the ability to modify the number of the OH contact points with the cavity - generally between 3 and 8 - it is possible to design host sites that can accept a wide variety of three-dimensional metal ions and organic guests structures with both high selectivity and strength. Shinkai cell this process "chemirecongnics".

*Research Strategy*

This project is exploring the basic relationships between the molecular structures of hosts - calixarene and other intelligent compounds - and their recognition properties. Through modifications, an attempt is also being made to design "artificial" recognition systems with very high recognition of and selectivity towards alkaline and rare earth metal ions and organic molecules. Sugars are especially challenging and important organic molecules. These efforts are not being limited to particular hosts, like those found in nature, but include entirely new recognition mechanisms as well as recognition targets, while also aiming to control (switch) the activity of the receptors.

This project is thus studying calixarenes and other compounds with the aim of establishing a high-precision chemirecognition system by introducing into these compounds: 1) an interface for binding with a specific guest atom or molecule, 2) a transducer for the information transduction, and 3) a stimulation receptor for "on-off" controlling the interface and transducer. Theoretical computer calculations are being made to support the design of such recognition systems. By establishing methodologies for designing recognition, superior molecular sensors and artificial enzymes with high selectivity, environmental resistance and utility may be produced-all in artificial systems.

*Research Progress*

o Calixarene was modified in such a way that allowed an extraordinary quantum jump in selectivity (from about 103 to 105) of Na with respect to K. The success of this method was to reverse a clever method of nature. Since the only way to discriminate between physically similar alkaline metals is by size, in nature the antibiotic valinomycin can recognize Na against K by using a bigger ionophore which also fits to Rb. Though the affinity to K is slightly reduced, the affinity towards Na is only slightly decreased, but the selectivity is greatly increased. Thus, by designing a very small cavity as the "interface" - with a size between that of Li and Na - using calixarene capped with a 4-oxygen crown-type loop, a cavity with a very large affinity towards Na was obtained.

o It has been found that the $C_{60}$ fullerene can be separated from other fullerenes in a carbon-powder soot using calixarene. Interestingly, calixarene is the third ring-type supramolecule and $C_{60}$ is the third type carbon cluster, after diamond and graphite. This method produces a 1-to-1 complex Of $C_{60}$ and calix[8]arene. Surprisingly, when $C_{60}$ enters the cavity of calix[8]arene it disrupts the intermolecular hydrogen bonding of the OH groups, causing the host to suddenly

change from soluble to insoluble in such a solvent as toluene. By collecting the precipitated $C_{60}$ and calix[8]arene complex and then putting it into chloroform, which has an even higher affinity to the host, it replaces the $C_{60}$ which is precipitated in 70% yield and 99.8% purity. This new method has greatly reduced the separation costs by possibly 1/50 or so while making the standard method, chromatography, obsolete.

o Other than calixarenes, cholesterol and boronic-acid moieties could be used as platforms of "intelligent" recognition. Since cholesterol forms a helical structure, the stability and related aggregation structure could be controlled by introducing certain substitutes and changing the C-3 position. It was also found that the cholesterol boronic-acid derivative can be applied to the recognition and optical resolution of saccharides (sugars). A saccharide and a cholesterol boronic acid compound form a 1:2 complex with a different steric structure, depending on the type of saccharide used. Upon the addition of such a complex to a cholestelic liquid crystal, the stability of the helical structure of the liquid crystal is differently affected by the structure of the complex, as a "transducer", thus producing a different color change depending on the type of saccharide of the complex.

## 21) Tonomura Electron Wavefront (1989-1994)

### *Backgound*

One of the most interesting and important phenomenon of science is the information that can be carried by and obtained from waves. After all, it is through the analysis of various types of particle-waves scattered by atoms, molecules and surfaces that vastly interesting and hitherto unknown details of the microcosm are being uncovered.

With the advent of lasers capable of producing highly coherent light beams it became possible to take full advantage of the phase nature of light to make direct observations. At that time electron microscopy was thought to have reached its capability Emits. This perspective significantly changed when it came to be learned that advanced field-emission techniques could produce electrons in very bright, fairly coherent beams. Akira Tonomura quickly took advantage of this fact in developing applications to electron microscopy: by using an electron biplism to manipulate coherent electron beams, it has become possible to realize an immensely powerful technique called "electron holography".

Thus, electron interference fringes have become easily observable with a field-emission electron beam that can produce as many as 3,000 interference fringes. Not only is it now possible to directly observe many molecular- and atomic-level phenomena, but this technology is becoming highly useful in fundamental physics. Two outstanding examples are Tonomura's use of electron holography to confirm the famous Aharonov-Bohm (AB) effect and to directly visualize magnetic fields.

### *Research Strategy*

The Electron Wavefront Project is attempting to greatly extend the use of the wave nature - phase - of electron beams to observe both the physical and electronic structures of microscopic and ultra-microscopic samples, while making visible many things which are beyond current observational capabilities.

One area of interest involves investigations of the basic nature of coherent electron beams, especially how they differ from coherent light beams. Such information should greatly help in designing practical experiments using electron holography, where it will be necessary to rapidly

measure phase changes in electron waves to a precision of 1/100 of a wavelength. (An electron passing through one atomic layer of material undergoes a phase shift of approximately 1/100 of its wavelength.)

This work is also very much concerned with finding a variety of applications of electron holography to studies of basic physics. The various techniques which use electron holography are providing very unique tools for resolving many of the lingering thought (gedanken) experiments that form the theoretical-philosophical bases of quantum mechanics.

An exploration of the basic interference properties and related phase distribution patterns of electron waves is also being carried out, so as to be able to extract information concerning material structures and electromagnetic field distributions in three dimensions from electron phase measurements. Thus, efforts are being made to develop high-precision real-time digital image-analysis methods using supercomputers.

Finally, high-precision electron phase measurements are being applied to both practical physics and biology, while endeavoring to make atomic-level observations of biopolymers such as DNA and of high technology materials such as semiconductors. Special cooling technologies are being applied so as to protect delicate living structures, such as cells and DNA during observations.

***Research Progress***

o The movement of fluxons trapped in a thin superconducting film has been observed for the first time. After trapping the fluxons by cooling a thin tungsten wire coated with 0.7 gm of lead from 8K to 5K in a magnetic field, they were recorded on videotape using electron holography. The real-time interference patters were then digitized and stored in a computer. By Fourier transforming this data, the phase pattern, and thus the magnetic field pattern, could be reconstructed. The produced images were then numerically cleaned, producing very sharp images of the trapped fluxons.

o Electron holography has a potential of overcoming the resolution limitation of an electron microscope due to the spherical aberration of an electron lens. A new method for correcting the aberrations of the objective lens at the holographic reconstruction stage is proposed. In this method, a liquid-crystal spatial-light modulator (LC-SLM) is used as a computer-controlled phase plate in the Fourier-plane of the optical reconstruction system. The effective refractive index of the liquid crystal can be changed by the applied electric field owing to its birefringent property. Hence, the phase of light passing through the LC-SLM can be flexibly modulated to compensate for any aberrations.

**22) Aono Atomcraft (1989-1994)**

***Background***

During the course of science and technology various new materials have been created which do not exist in nature: metal alloys and both organic and inorganic compounds with novel atomic arrangements are good examples. Their many useful functions have been subsequently greatly used. Today, even superlattices can be created by technologically controlling the growth of films at the level of atomic layers. Still, the ultimate dream of materials scientists is to create new functional materials by controlling their atomic arrangements through the manipulation of single atoms.

The word "atomcraft," used as the name of this project, was coined in order to express a

new dimension of atomic-scale science and technology in which single-atom manipulation is effectively used, including the creation of new materials with customized atomic arrangements which exhibit novel properties, and nanometer-size electrode arrangements which show novel functions as electrolytic devices. Although only a dream a decade ago, this is now a promising field, thanks to the invention of the scanning tunneling microscope (STM), which can be used not only to observe atoms, but to also manipulate them. In fact, several preliminary demonstrations suggest the power of this approach. Challenges remain, however, in understanding the physical mechanisms involved and in the many issues related to technological feasibility. This project has been organized to perform systematic studies in order to overcome such hurdles and to apply the results to the above-mentioned fields.

*Research Strategy*

In this project great importance is attached to a close cooperation between experimentalists and theorists. The, theorists are not only carrying out various calculations in order to interpret the obtained experimental results, but are also designing promising experiments.

Emphasis is being placed on the development of various reliable new techniques to extract, deposit, and displace single atoms at will. For this purpose, it is essential to clearly understand the physical mechanisms involved. It is also important to routinely prepare desired tips for atoms manipulation and to control atom movement and electrical parameters in a sophisticated manner.

It is also necessary to directly measure the various properties and functions of the various new artificial materials created, as well as nanometer-scale electrode arrangements over a range of temperatures. New methods are being developed for these purposes.

*Research Progress*

o A technique has been developed to extract single silicon atoms from predetermined positions of a "Si(111)-7x7" sample surface. Using this technique it is possible to create any pattern of silicon atom vacancies on a sample surface. Larger fabrication, such as the creation of grooves with a width of a few nanometers, is also possible by changing the electric parameters applied to the tip and by scanning the tip parallel to the sample surface. The physical mechanisms involved in this atom extraction have been clarified and the mechanisms verified through theoretical calculations.

o It has been found that atom extraction from different sites strongly depends on the binding energies of the atoms. There is a fairly simple relationship between the probability of atom extraction and the atom binding energy, which should be very useful in future well-controlled atomic-scale material structure fabrication. Conversely, it is now possible to probe differences of atom binding energies through such experiments.

o It has also been found that the extracted silicon atoms mentioned above can be redeposited onto a sample surface by appropriately selecting the electric parameters applied to the tip. For example, by using this technique, originally existing silicon vacancy defects on sample surfaces have been repaired. It has also been found that redeposited silicon atoms on a sample surface can be intentionally displaced using the tip. This is the first demonstration of atom displacement which is stable at room temperature.

o A single-electron charging effect, called "the Coulomb blockade," has been observed at room temperature for the first time for a three-electrode system in which the outer two electrodes are an STM tip and a platinum substrate and the intermediate electrodes are liquid crystal molecules. This indicates that single-electron tunneling transistors working at room temperature

can be realized in the future.

## 23) Ikeda GenoSPHERE (1989-1994)

*Background*

All of the life processes and characteristics of an organism depend on the genetic information - the genome - contained in its cells. Though for many years it has been generally considered that the genome is mainly expressed in terms of the component genes, Joh-E Ikeda is exploring the idea that equally important is the geometry of their folding into chromosomes - considered to be organic complexes - and the position orientation and interrelationship of the various chromosomes within the cell. Ikeda has thus coined the word "Genosphere" to refer to genes and the chromosomes as well as their surroundings and interactions, a holistic perspective on the cellular scale.

The central theme of the Genosphere Project is to obtain a greater understanding of the significance that chromosomes, as opposed to component genes, play in determining the biochemistry of cells as well as the growth, development and maintenance of organisms as a whole. In short, a new field of chromosome engineering is being pursued.

*Research Strategy*

Major components of this project are to identify: 1) the genes, 2) chromosome domains responsible for genomic functions, 3) gene products and 4) behavior related to various biological activities, including neural. To this end, specific portions of chromosomes are being dissected. They are then segmented according to chromosome maps and studied. Further, they are introduced into the genospheres of other chromosomes while observing where they join. The enzymes and other molecules that are involved in this procedure are also being studied.

Since many aspects of an organism's health and well being are determined by the physical-chemical condition of the genome, often established during embryogenesis, latent disease, and even the phenomenon of aging, might well be related to specific genetic weaknesses that make themselves manifest with time. A second area of research therefore involves the isolation of specific chromosome segments containing genetical disease genes related to mental defects using chromosome maps.

In order to fully develop this research program, new instruments are being developed which will allow constant monitoring of the chromosomes within cells regarding their relative positions and orientations within cellular nuclei, as well as changes within time. Also observable will be how an added chromosome segment determines its location within the genosphere of a nucleus. These new optical devices will hopefully result in real-time three-dimensional maps of chromosome positions.

*Research Progress*

o In an effort to isolate specific segments of chromosome for analysis an instrument has already been constructs that uses a sophisticated combination of microscope, argonion laser and computer software, called a "laser chromosome micro-dissector". Using this fully automated equipment a slide carrying many chromosomes and other materials can be systematically cleared of all large molecules by laser cutting to sub-micron (=O.3gm) accuracy, leaven the very specific chromosome part that is to be studied.

o The chromosome microdissection technique has been used in conjunction with a

polymerase chain reaction (PCR) approach to directly amplify microdissected chromosome This microdissection and PCR cloning procedure comprise a simple and general approach for constructing a chromosome region-specific DNA library from a single metaphase spread. These methods were applied to the distal half of the short arm of human chromosome 4 containing the Huntington disease (HD) locus and the terminal end of the long arm of human chromosome X where many mental faculty related genes have been mapped.

o An improvement has been made to the dot-matrix similarity plot technique which provides a visual representation of sequence relatedness to compare biological sequences. The improvement involves the compilation of a data structure known as a position tree, which provides a lexical index to the sequences and is compiled in time linear with the sequence length.

o A regional genomic library of the distal 30% of the long arm of the human X chromosome was constructed from a single metaphase spread by means of laser microdissection and Single Unique Primer (SLTP)-PCR. Using pooled probes of 1000 clones from the genomic library, human brain cDNA libraries were screened for isolation of expressed sequences encoded by this region. Out of 250,000 phases of the cDNA libraries so far screened, 10 nonoverlapping sequences were isolated that mapped back to the target portion. Nucleotide sequences of those cDNA clones were determined. Analysis of the sequences suggested that none of them have significant similarities to the cloned primate genes. Open reading frames were detected from two clones that mapped to Xq27.3qter.

**Table 1: List of Active ERATO Projects**
**(in reverse chronological order)**

| Period | Research Topic | Project Leader(affiliation) |
|---|---|---|
| 1994-1999 | Particle Surface | Prof. Kunio Takayanagi (Tokyo Institute of Tech.) |
| 1994-1999 | Active Glass | Prof Kazuyuki Hirao (Kyoto University) |
| 1994-1999 | Behavior Genes | Dr. Daisuke Yamamoto (Mitsubishi Chemical) |
| 1994-1999 | Biotimer | Prof. Yoshimi Takai (Osaka University) |
| 1993-1998 | Quantum Fluctuation | Dr. Yoshihisa Yamamoto (NTT Basic Research Labs) |
| 1993-1998 | Solid Junction | Dr. Shun-ichiro Tanaka (Toshiba Corporation) |
| 1993-1998 | Polymer Phasing | Prof. Takeji Hashimoto (Kyoto University) |
| 1993-1998 | Cell-Configuration | Dr. Setsuo Hirohashi (National Cancer Center Research Institute) |
| 1992-1997 | Millibioflight | Prof. Kenji Kawachi (University of Tokyo) |
| 1992-1997 | Electrochemiscopy | Prof. Kingo Itaya (Tohoku University) |
| 1992-1997 | Biomotron | Prof. Toshio Yanagida (Osaka University) |
| 1992-1997 | MorphoMatrix | Prof Katsutoshi Yoshizato (Hiroshima University) |
| 1991-1996 | Pi-Electron Materials | Dr. Susumu Yoshimura (Mastushita Research Inst.) |
| 1991-1996 | Molecular Catalysis | Prof. Ryoji Noyori (Nagoya Unversity) |
| 1991-1996 | Biofouling | Prof. Nobuhiro Fusetani (University of Tokyo) |
| 1991-1996 | Cell Switching | Prof. Hiroto Okayama (University of Tokyo) |
| 1990-1995 | Metamelt | Dr. Shigeyuki Kimura (NIRIM, STA) |
| 1990-1995 | Protein Array | Prof. Kuniaki Nagayama (University of Tokyo) |
| 1990-1995 | Nutrient-stasis | Dr. Kunio Torii (Ajinomoto Co., Inc.) |
| 1990-1995 | Chemirecognics | Prof. Seji Shinkai (Kyushu University) |
| 1989-1994 | Electron Wavafront | Dr. Akira Tonomura (HITACHI Ltd.) |
| 1989-1994 | Atomcraft | Dr. Masakazu Aono (RIKEN) |
| 1989-1994 | GenoSPHERE | Prof. Jon-E Ikeda (Tokai University) |

**Table 2: List of Completed ERATO Projects**
**(in reverse chronological order)**

| Period | Research Topic | Project Leader(affiliation) |
|---|---|---|
| 1988-1993 | Quantum Wave | Prof. Hiroyuki Sakaki (University of Tokyo) |
| 1988-1993 | Microphotoconversion | Prof. Hiroshi Masuhara (Osaka University) |
| 1988-1993 | Plant Ecochemicals | Prof. Junya Mizutani (Hokkaido University) |
| 1987-1992 | Terahertz | Prof. Jun-ichi Nishizawa (Tohoku University) |
| 1987-1992 | MorphoGenes | Dr. Mitsuru Furusawa (Daiichi Paharmaceutical Co.) |
| 1987-1992 | Molecular Architecture | Prof. Toyoki Kunitake (Kyushu University) |
| 1986-1991 | Quantum Magneto Flux Logic | Prof Eiichi Goto (Kanagawa University) |
| 1986-1991 | Molecular Dynamic Assembly | Prof. Hirokazu Hotani (Tokyo University) |
| 1986-1991 | Biophoton | Prof. Humio Inaba (Tohoku University) |
| 1985-1990 | Nano-Mechanism | Mr. Shoichiro Yashida (NIKON Corporation) |
| 1985-1990 | Solid Surface | Prof. Haruo Kuroda (University of Tokyo) |
| 1984-1989 | Superbugs | Prof Koki Horikoshi (Tokyo Institute of Technology) |
| 1983-1988 | Bioinformation Transfer | Dr. Osamu Hayashi (Osaka Bioscience Institute) |
| 1982-1987 | Bioholonics | Prof. Den'ichi Mizuno (Teikyo University) |
| 1981-1986 | Ultra-Fine Particle | Dr. Chikara Hayashi (ULVAC Corporation) |
| 1981-1986 | Amorphous & Intercalation Compounds | Prof. Tsuyoshi Masumoto (Tohoku University) |
| 1981-1986 | Fine Polymer | Prof. Naoya Ogata (Sophia University) |
| 1981-1986 | Perfect Crystal | Prof. Jun-ichi Nishizawa (Tohoku University) |